XXVI.—*Phthaleins and Fluorans.*

By MAURICE COPISAROW.

THE object of this investigation was the study of the constitution and conditions of formation of some members of the phthalein and fluoran series. Whilst certain phenols, such as resorcinol and pyrogallol, react with phthalic anhydride in the absence of any dehydrating agent, in most other cases some such agent is required for the condensation to take place. These condensing agents, in conjunction with the experimental conditions, influence not only the yield, but also the character of the products. In most cases, the formation of phthaleins (III) is accompanied by the production of substances belonging to the *o*-ketonic acid (I) (Deichler and Weizmann, *Ber.*, 1903, **36**, 547; Copisarow and Weizmann, *T.*, 1915, **107**, 878), hydroxyanthraquinone (II), and fluoran (IV) series.

It is probable that when aluminium chloride is employed as a condensing agent, the products just quoted are accompanied

by small quantities of substances belonging to the phenyl-oxanthranol (V), tetraphenylmethane-*o*-carboxylic acid (VI), and diphenylanthrone (VII) series (Copisarow, T., 1917, **111**, 10).

On replacing phthalic anhydride by phthalyl chloride, isophthaleins or phenolic esters of phthalic acid are formed (Baeyer, *Ber.*, 1871, **4**, 659; Meyer, *Ber.*, 1891, **24**, 1414; 1893, **26**, 204; 1895, **28**, 431; Pawlewski, *Ber.*, 1895, **28**, 108, 2360; Limpicht, *Annalen*, 1898, **303**, 279; Csányi, *Ber.*, 1919, **52**, 1788).

In the course of the present investigation, it was found that:

(1) Hydrogen chloride, as a condensing agent, facilitates the formation of hydroxyanthraquinones and phthaleins.

(2) Boric acid, as a condensing agent, assists the formation, not only of *o*-ketonic acids and hydroxyanthraquinones (Deichler and Weizmann, *loc. cit.*), but also that of phthaleins and fluorans.

(3) Hydrogen chloride is most efficient in the presence of zinc chloride, and boric acid in the presence of concentrated sulphuric acid.

(4) The hydroxy-groups of the phthaleins are, as a rule, in the para-position, and of the fluorans in the ortho-position, with respect to the central carbon atom linking the phthaloyl with the phenolic groups. This is proved by (a) the fact that phenolphthalein is not converted into fluoran on heating above its melting point or with concentrated sulphuric and boric acids; (b) the non-formation of 4:5-dimethylfluoran, *p*-cresolphthalein, and β -naphtholphthalein; (c) the fact that boric acid exercises in the case of termolecular reactions (fluoran formation) the same orientating effect as in the case of bimolecular reactions (Bentley, Gardner, and Weizmann, T., 1907, **91**, 1626); this is substantiated, not only by the constitution of the fluorans, but also by the fact that the *o*-ketonic acids are an intermediate stage in the formation of fluorans from phthalic anhydride, as in the case of phthalides (Pechmann, *Ber.*, 1881, **14**, 1865; Copisarow and Weizmann, *loc. cit.*).

The apparently anomalous position of α -naphtholphthalein, prepared by the hydrolysis of di-1-ethoxynaphthylphthalide, in which Copisarow and Weizmann (*loc. cit.*) assigned the hydroxy-groups to the ortho-position with respect to the central carbon atom, on the ground that *o*-1-ethoxynaphthoylbenzoic acid can be regarded as an intermediate stage between phthalyl chloride and di-1-ethoxynaphthylphthalide, and also owing to the transformation of this α -naphtholphthalein into α -naphthafluoran, can now be easily explained.

Grabowski (*Ber.*, 1871, **4**, 661), and Sørensen and Palitzsch (*Biochem. Zeitsch.*, 1910, **24**, 384), have indicated the possible formation of two isomeric α -naphtholphthaleins, and considering

that (a) Grabowski's α -naphtholphthalein cannot be converted into α -naphthfluoran, thus differing from Copisarow and Weizmann's o - α -naphtholphthalein, and (b) the α -naphtholphthalein isolated by Csányi (*loc. cit.*) is identical with that of Copisarow and Weizmann (a sample preserved from 1915 and recrystallised twice from alcohol melted at 234—235°), there is no room for doubt that the following constitutions must be assigned to the two existing α -naphtholphthaleins:

(VIII.)

p- α -Naphtholphthalein.
(Grabowski.)

(IX.)

o- α -Naphtholphthalein.
(Copisarow and Weizmann, Csányi)

(5) Zinc chloride, as a condensing agent, is found to be superior to both concentrated sulphuric acid and stannic chloride, being more efficient than the former and more economical than the latter.

It was found that the alkali salts of the phthaleins, like those of phenols, are oxidised on prolonged keeping, especially on exposure to light or a current of air, giving dark, complex substances. The alkaline earth salts (barium, calcium, etc.) are less readily oxidised.

EXPERIMENTAL.

Zinc Chloride.

It was found that zinc chloride, prepared by evaporating to dryness a faintly acid solution of this salt, is a more efficient condensing agent than finely powdered fused sticks of zinc chloride. This superior quality is to be attributed to the fineness of division and presence of small quantities of hydrogen chloride rather than to the possible hydration of the unfused zinc chloride (compare aluminium chloride, Biltz, *Ber.*, 1893, **26**, 1960; Meyer, *Ber.*, 1896, **29**, 847), as the addition of small quantities of water to the fused zinc chloride not only does not add to, but actually diminishes, its efficiency.

Phenolphthalein (III).

Preparation by means of Concentrated Sulphuric Acid.—The condensation of phthalic anhydride with phenol in the presence of concentrated sulphuric acid was effected under the conditions given by Baeyer (*Annalen*, 1880, **202**, 69). It was found, however, that by employing an improved method of isolation and purification, the product contains about 5 per cent. of hydroxyanthraquinones. Baeyer's method of purification, consisting in pouring the decolorised alcoholic solution of the product into water, is thus ineffective. A more satisfactory method was found to be as follows.

The crude phenolphthalein, having been dissolved in aqueous sodium hydroxide and reprecipitated with hydrochloric acid, is dissolved in five times its weight of 65–70 per cent. methyl alcohol. The alcoholic solution is decolorised by boiling with animal charcoal and concentrated until solid begins to separate. On cooling and filtering, the first crop of phenolphthalein (yellow to white) is obtained; a second crop of this product is isolated on concentrating the filtrate. On further distillation, an orange-red, viscid oil separates, which, on keeping, solidifies to a brown, crystalline mass consisting of the two isomeric hydroxyanthraquinones and some phenolphthalein. The first two crops of phenolphthalein, when recrystallised from dilute alcohol, furnish snow-white crystals melting at 253°. This method of purification gives, not only phenolphthalein free from hydroxyanthraquinones, but also appears to be less wasteful than that of Baeyer, as more than 90 per cent. of the solvent is recovered. The separation of the two isomeric hydroxyanthraquinones from one another was effected according to Baeyer and Caro's method (*Ber.*, 1874, **7**, 969). The phenolphthalein accompanying the hydroxyanthraquinones is isolated by fractional crystallisation. The yield of pure phenolphthalein obtained by this method is 26 per cent. of that theoretically possible. The yield of fluoran (IV) (Baeyer, *Annalen*, 1882, **212**, 347) does not exceed 0.5 per cent.

Preparation by means of Concentrated Sulphuric and Boric Acids.—A mixture of 60 grams (1 mol.) of finely powdered phthalic anhydride, 80 grams (2 mols.) of phenol, 16 grams of concentrated sulphuric acid, and 8 grams of powdered boric acid was heated at 125–130° for eight hours. The product was poured into water, the mixture boiled to expel phenol, filtered while hot, and the brown residue washed with hot water. The residue was extracted several times with a 3 per cent. solution of sodium hydroxide, the extract cooled, and acidified with hydrochloric acid. The pre-

cipitate, which contained phenolphthalein and the hydroxyanthraquinones, was purified as in the previous experiment. The residue, insoluble in sodium hydroxide, crystallised from alcohol in white, rhombic crystals melting at 173—175°, and consisted of fluoran. The yield of pure phenolphthalein was 31 per cent., that of fluoran 8 per cent., and that of the hydroxyanthraquinones about 5 per cent. of the theoretical. No advantage was gained by employing boric anhydride instead of boric acid. The latter in the absence of concentrated sulphuric acid is ineffective as a condensing agent under the conditions employed.

Preparation by means of Zinc Chloride.—The conditions of condensation were those described by Perkin and Kipping ("Organic Chemistry," 1911, 654), the mixture being mechanically stirred. The method of purification of the products was identical with that already described. The yield of pure phenolphthalein was 47 per cent., and that of the two hydroxyanthraquinones 6 per cent., of the theoretical. The yield of fluoran was negligible. When powdered fused zinc chloride was employed, instead of zinc chloride prepared by the method described above, the yield of the products was lowered.

Preparation by means of Hydrogen Chloride.—From analogy to the formation of esters, it was considered possible that hydrogen chloride might serve as a condensing agent for the production of phthaleins. Investigation showed that whilst hydrogen chloride by itself is not sufficiently effective, taken in conjunction with zinc chloride, a marked improvement in the yield of phenolphthalein, and especially of the hydroxyanthraquinones, was observed. The following table shows the results of condensation by means of dry hydrogen chloride.

Experi- ment.	Phthalic anhydride. Gram- mols.	Phenol. Gram- mols.	Period of heating, in hours.	Period of passing a current of hydrogen chloride, in hours.	Yield, per cent.	Colour.
1	1	2	6.0	0.5	0.2	greyish brown
2	1	2	6.0	6.0	0.9	dark brown
3	1	4	6.0	6.0	0.8	"
4	1	2	24.0	24.0	1.7	"

These reactions were carried out at 120—125°, the method of isolation and purification of the products being the same as in the experiments already described. The ratio of phenolphthalein to the hydroxyanthraquinones was found to be approximately 1 to 1. No fluoran was found. When the temperature was raised to 170°, the proportion of the hydroxyanthraquinones and tarry matter was increased. The results indicate that (1) the yield of product

increases with the period of heating in a current of hydrogen chloride, and (2) the ratio of phenol to phthalic anhydride does not influence the yield.

These observations show a distinct difference between phthaleins and esters as regards the mechanism of their formation.

Preparation by means of Zinc Chloride and Hydrogen Chloride.

—A current of dry hydrogen chloride was passed through a mixture of 60 grams of finely powdered phthalic anhydride, 70 grams of zinc chloride, and 80 grams of phenol at 120—125° for half an hour, the mixture being then heated for six hours at 120—125°. The product was poured into water, which was boiled to expel phenol. The mixture was then filtered hot, washed with hot water, and the yellowish-brown residue extracted several times with a warm 4—5 per cent. solution of sodium hydroxide. The deep red alkaline solution was cooled and acidified with hydrochloric acid, and the precipitate collected, pressed, and dried. The quantity of material insoluble in alkali did not exceed 0.5 per cent. The dried precipitate was purified by decolorising with animal charcoal and fractional crystallisation from 65 per cent. methyl alcohol, as described in previous experiments. On concentrating the filtrate after the isolation of two crops of phenolphthalein, a brownish-red, viscid oil separated, which solidified on keeping. This contained hydroxyanthraquinones and phenolphthalein, the latter being about 33 per cent. of the total. The yield of pure phenolphthalein from the two crops was 52 per cent., and that of the hydroxyanthraquinones 21 per cent., the total yield of phenolphthalein being 59 per cent. of the theoretical; the 7 per cent. of phenolphthalein present in the oily residue was isolated only by a lengthy process of separation from the two hydroxyanthraquinones and fractional crystallisation, as already described. This fraction of phenolphthalein may therefore be disregarded in calculating the efficiency of this method of preparation. In subsequent experiments, the employment of hydrogen chloride was omitted.

When pure phenolphthalein is heated (*a*) above its melting point, or (*b*) with concentrated sulphuric and boric acids at 125—130° for eight hours, no fluoran is formed.

Baeyer (*Annalen*, 1880, **202**, 153) describes the employment of concentrated sulphuric acid and stannic chloride in the condensa-

tion of phthalic anhydride with *o*-cresol, but no indication is given either of the by-products formed or of the efficiency of each condensing agent. When phthalic anhydride was condensed with *o*-cresol in the presence of concentrated sulphuric acid under the conditions given by Baeyer, the yield was poor. A distinct improvement in yield, although this was still low, was achieved by using a mixture of concentrated sulphuric and boric acids. No 4:5-dimethylfluoran could be detected.

Preparation by means of Zinc Chloride.—Fifteen grams of phthalic anhydride and 25 grams of zinc chloride were finely powdered, 25 grams of *o*-cresol added, and the mixture was heated at 125° for eight hours. The product was worked up as in the previous experiments. On fractionally crystallising the crude precipitate from dilute alcohol, 16 grams (46 per cent. of the theoretical yield) of *o*-cresolphthalein were obtained in yellowish-white crystals melting at 216°. The last crop, fractionated by crystallising from acetic acid, was found to consist of 1-hydroxy-2-methylantraquinone, melting at 184—185° (Bentley, Gardner, and Weizmann, T., 1907, **91**, 1634), 3-hydroxy-2-methylantraquinone, melting at 262° (Baeyer, *Annalen*, 1880, **202**, 165), and a small quantity of *o*-cresolphthalein. No 2-hydroxy-1-methylantraquinone could be detected. The combined yield of the two anthraquinones was about 4 per cent. of the theoretical.

The condensation of phthalic anhydride with *p*-cresol in the presence of zinc chloride was carried out in a manner similar to that employed in the case of *o*-cresol. The product, freed from *p*-cresol, phthalic acid, and zinc chloride, was extracted several times with dilute sodium hydroxide solution, and the dried residue decolorised with animal charcoal and crystallised from chloroform. It separated in yellowish-white crystals melting at 246°, and was identified as 2:7-dimethylfluoran (Baeyer, *Annalen*, 1882, **212**, 340). The brownish-red alkaline extract was acidified with hydrochloric acid, and the precipitate crystallised from glacial acetic acid in brownish-yellow needles melting at 169—170°, which were identified as 4-hydroxy-1-methylantraquinone (Birukoff, *Ber.*,

1887, **20**, 2069). The yield of 2:7-dimethylfluoran was 26 per cent., and that of 4-hydroxy-1-methylantraquinone 2.5 per cent., of the theoretical. No trace of *p*-cresolphthalein could be detected.

p- α - and *o*- α -Naphtholphthaleins (VIII and IX) and α -Naphtha-

Preparation by means of Zinc Chloride.—The condensation of phthalic anhydride with α -naphthol in the presence of zinc chloride results in the formation of *o*- and *p*- α -naphtholphthaleins, α -naphthafluoran, and small quantities of α -hydroxynaphthacenequinone. Five grams of phthalic anhydride, 10 grams of α -naphthol, and 15 grams of zinc chloride were finely powdered, thoroughly mixed, and heated in a flask immersed in an oil-bath at 100° for three hours. The product was extracted several times with boiling water, and then with a dilute solution of sodium hydroxide. The insoluble residue separated from benzene in small, white crystals melting at 300°, and was identified as α -naphthafluoran (Grabowski, *Ber.*, 1871, **4**, 661; Meyer, *Ber.*, 1893, **26**, 207; Deichler and Weizmann, *Ber.*, 1903, **36**, 548). The deep bluish-green, alkaline extract was fractionally precipitated with hydrochloric acid and carbon dioxide according to Werner's method (T., 1918, **113**, 20). The dried precipitate was extracted with benzene, from which, on keeping, brownish-yellow crystals melting at 209° separated. This substance was identified as *p*- α -naphtholphthalein (Grabowski, *Ber.*, 1871, **4**, 725; 1873, **6**, 1065). It gives a deep blue coloration with alkalis, and is not converted into α -naphthafluoran on heating above its melting point or with concentrated sulphuric and boric acids. On keeping the benzene mother liquors, a small quantity (about 1 per cent.) of α -hydroxynaphthacenequinone (Deichler and Weizmann, *loc. cit.*; D.R.-P. 134985) was isolated in orange-red needles melting at 303°. The residue left after extracting the precipitate with benzene dissolved in ethyl alcohol, from which it separated in pinkish-yellow, prismatic needles melting at 234—235°. This substance was identified as *o*- α -naphtholphthalein (Copisarow and Weizmann, *loc. cit.*;

Csányi, *loc. cit.*). It gives a deep green coloration (probably due to the *o*-quinonoid structure) with alkalis, and is converted into α -naphthafluoran on heating above its melting point or with concentrated sulphuric and boric acids. In this condensation, the yield of crude α -naphtholphthalein (dried precipitate) was 45 per cent., whilst that of α -naphthafluoran was 20 per cent., of the theoretical. The proportion of *p*- α - to *o*- α -naphtholphthalein is about 4 to 1. When the period of heating was reduced from three hours to one, the yield of crude α -naphtholphthalein was increased to 50 per cent., and that of α -naphthafluoran reduced to 17.3 per cent. The best yield was obtained by heating an intimate mixture of phthalic anhydride, α -naphthol, and zinc chloride in a shallow basin in an air-oven at 100° for half an hour. The yield of α -naphtholphthalein reached 59.3 per cent., and that of α -naphthafluoran 30 per cent., of the theoretical. Sørensen and Palitzsch (*loc. cit.*) obtained a 20.7 per cent. yield of α -naphtholphthalein by heating phthalyl chloride with α -naphthol, whilst Werner (*loc. cit.*), carrying out the condensation of phthalic anhydride with α -naphthol in the presence of concentrated sulphuric acid, found the yield to be 22.4 per cent. of the theoretical, the yield of α -naphthafluoran being very small.

A mixture of 14.8 grams of phthalic anhydride, 30 grams of zinc chloride, and 28.8 grams of β -naphthol was heated for four hours at 100°. The product was extracted several times with boiling water and then with a hot dilute solution of sodium hydroxide. On acidifying the brownish-red, alkaline extract, a brown precipitate was obtained, which, owing to its minute quantity, could not be investigated. From analogy to other condensations, this precipitate was probably the corresponding quinone. The residue insoluble in alkalis, after being crystallised from acetic acid, melted at 293°, and was identified as β -naphthafluoran (Meyer, *Ber.*, 1891, **24**, 1414; 1893, **26**, 206). The yield was 12.5 per cent. of the theoretical, as compared with 7 per cent. obtained by Meyer.

The straight-line configuration for β -naphthafluoran may be accepted as the more probable one, for reasons similar to those

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advanced in the case of phthaloyl- and diphtaloyl-carbazoles (Copisarow and Weizmann, *loc. cit.*).

The formation by α -naphthol of phthaleins which give intensely coloured sensitive alkaline salts, and the failure of β -naphthol to form a phthalein, may be used as a colour reaction for identifying small quantities of α -naphthol in β -naphthol.

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CHEMICAL DEPARTMENT,
THE UNIVERSITY,
MANCHESTER.

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